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Original Research

Valuing preferences for treating screen detected ductal carcinoma *in situ*

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Abstract

***Background*:** Mammographic screening reduces breast cancer mortality but may lead to the overdiagnosis and overtreatment of low-risk breast cancers. Conservative management may reduce the potential harm of overtreatment, yet little is known about the impact upon quality of life.

***Objectives*:** To quantify women's preferences for managing low-risk screen detected ductal carcinoma *in situ* (DCIS), including the acceptability of active monitoring as an alternative treatment.

***Methods*:** Utilities (cardinal measures of quality of life) were elicited from 172 women using visual analogue scales (VASs), standard gambles, and the Euro-Qol-5D-5L questionnaire for seven health states describing treatments for low-risk DCIS. Socio-demographics and breast cancer history were examined as predictors of utility.

***Results*:** Both patients and non-patients valued active monitoring more favourably on average than conventional treatment. Utilities were lowest for DCIS treated with mastectomy (VAS: 0.454) or

breast conserving surgery (BCS) with adjuvant radiotherapy (VAS: 0.575). The utility of active monitoring was comparable to ~~breast conserving surgery~~BCS alone but was rated more favourably as progression risk was reduced from 40% to 10%. Disutility for active monitoring was likely driven by anxiety around progression, whereas conventional management impacted other dimensions of quality of life. The heterogeneity between individual preferences could not be explained by socio-demographic variables, suggesting that the factors influencing women's preferences are complex.

***Conclusions*:** Active monitoring of low-risk DCIS is likely to be an acceptable alternative for reducing the impact of overdiagnosis and overtreatment in terms of quality of life. Further research is required to determine sub-groups more likely to opt for conservative management.

Keywords: Breast cancer; Ductal carcinoma *in situ*; Active monitoring; Surgery; Radiotherapy; Utility; Quality of life

1 Introduction

Breast cancer screening reduces breast cancer morbidity and mortality [1,2] but may also lead to the overdiagnosis of low-risk disease [3]. Ductal carcinoma *in situ* (DCIS) is a heterogeneous disease with variable malignant potential [4], but it is not known which patients may be safely left untreated. Standard treatment encompasses surgery, with or without radiotherapy, and endocrine therapy [5]. There is evidence to suggest that active monitoring of low-risk DCIS (defined as low or low-intermediate grade on histopathology) may reduce treatment-related harm from overdiagnosis [6]. Clinical trials comparing conventional treatment to active monitoring are underway [7–9]. However, little is known about the acceptability of active monitoring or how such strategies may impact upon quality of life.

The value of treating DCIS versus active monitoring is dependent on the trade-off in benefits and costs [10,11]. For most women, this is related to the fear and sequalae of progression or recurrence versus the side-effects and morbidity of treatment [12]. ~~In order t~~To appraise the expected impact of each option on quality of life, utilities are an appropriate outcome measure [13]. Utilities are cardinal measures of quality of life [14], representing the strength of an individuals' preference for a health state or treatment. They are measured on a scale from 0 to 1, equivalent to being dead and in perfect health, respectively, and are used to measure benefit (quality-adjusted-life-years) in economic evaluations informing healthcare decisions [15].

Issues surrounding DCIS management arise from the uncertainty in disease progression. DCIS is not life-threatening but is a risk factor for developing invasive breast cancer [16]. Whilst surgery and radiotherapy may reduce the risk of invasive cancer and need for more invasive treatment if it does not progress, it is unlikely to have significant benefit upon survival [17]. Conversely, many women are exposed to the morbidity and costs of the initial treatment to reduce the risk of recurrence.

The objective of this study was to quantify women's preferences for managing low-risk DCIS identified by screening.

2 Methods

2.1 Health states

Utilities were elicited for seven hypothetical health states describing treatments for low-risk DCIS: (A) breast conserving surgery (BCS) alone, (B) BCS with radiotherapy, (C) mastectomy +/- reconstruction, (D) active monitoring with 40% risk of progression in 10 years, (E) active monitoring with 20% risk of progression in 10 years, (F) active monitoring with 10% risk of progression in 10 years and (G) treatment for progressed DCIS.

Health states were defined in a series of vignettes representing the treatments and clinical consequences associated with DCIS diagnosed at screening (Supplementary file). Descriptions were developed from clinical guidelines, systematic literature review [18], and consultation with clinicians. The risk of overdiagnosis and cancer progression was~~ere~~ explicitly included using three hypothetical estimates of breast cancer progression from meta-analyses [19] and recurrence rates after treatment from clinical trials [20]. Progressed DCIS was included to determine the magnitude of effect of an adverse outcome following surveillance. Endocrine treatment was optional for those with hormone positive disease.

Health states were unlabelled and used mixed framing to reduce bias in the presentation of potential benefits and risks [21]. Vignettes were piloted on patients to check content validity.

2.2 Eligibility

Utilities were obtained from women in Melbourne, Australia, between April and September 2018. Eligible women had to be aged over 30 years (breast cancer is uncommon below this threshold) and have basic oral and written English to complete the tasks. Both patient (DCIS/early invasive breast cancer) and non-patient (women without breast cancer) preferences were elicited, so values between groups with different disease knowledge could be explored. Women with advanced breast cancer or those undergoing active management (except for tamoxifen or aromatase inhibitors) were excluded.

2.3 Recruitment

Women were invited to participate by email invitation through the Lifepool cohort and Breast Cancer Network Australia's Review & Survey group. The two groups consist of registry of Australian members interested in participating in breast cancer research. Women were asked to contact the researchers if interested and were invited for interview. Additional women contacted the researchers through participant snowball sampling. All those who replied and met eligibility were included for sampling.

Individual interviews were undertaken at the University of Melbourne and local community facilities in Victoria. Two interviews were conducted via telecommunication to accommodate participants' disabilities. No financial incentive was provided. The study was approved by the Health Sciences Ethics Sub~~-C~~committee at the University of Melbourne (ID: 1750252).

2.4 Interviews

Women were interviewed face-to-face by a single interviewer (HB). The interview used an adaptation of the format described by Hayman *et al*. [22] and consisted of four parts: a rating scale, EuroQol-5 dimensions (EQ-5D)-5L, standard gamble and socio-demographic questionnaire (Supplementary File).

Participants were asked to read, in random order, seven hypothetical health states and rank them from least to most desirable on a 20 cm visual analogue scale, anchored from worst (0) to best (100) imaginable health. They were also asked to place being dead on the same scale so that health states could be adjusted to the dead-perfect health scale [15]. Second, participants were asked to rate the health states in terms of the five EQ-5D-5L [23] domains of quality of life (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Each dimension was divided into five hierarchical levels of severity, and scores were converted into utilities using general population tariffs [24].

For the standard gamble, participants were asked to choose between two alternatives: (i) a gamble between varying probabilities of perfect health and being dead or (ii) the health state being evaluated. The probabilities of the gamble were varied (ping-pong technique) until the participant was indifferent between the two alternatives, corresponding to the utility for the health state [25]. For comparability, participants were asked to consider that all states lasted 10-years in line with clinical trials of active monitoring [7]. Visual aids consisting of a chance board and probability wheel were used to aid comprehension [26]. Demographics were collected to enable subgroup and regression analyses.

2.5 Statistical analysis

Data analysis was carried out using STATA 14.0. The methods described by Hayman [27] were used to estimate a proxy sample size: the reported standard deviation of patient standard gamble~~SG~~ utilities is 0.2, thus requiring a minimum of 100 women for mean utilities to be estimated at a 95% confidence level of 0.04, with a power of 90%.

Differences in characteristics between patients and non-patients were analysed using t-tests and Chi-squared tests. Non-parametric tests were used to analyse utilities due to the non-normal distribution of the data [28]. Mann-Whitney U test was used to determine whether utilities differed between patient and non-patients. Correlation between methods was assessed using the Spearman's correlation coefficient and linear regression to determine if demographic variables were predictors of utility [29].

3 Results

3.1 Sample characteristics

A total of 929 women were invited and a further 36 women identified through snowball sampling. Out of 254 responses, 172 women (68%) completed the interview and were included in the analysis (Fig. 1).

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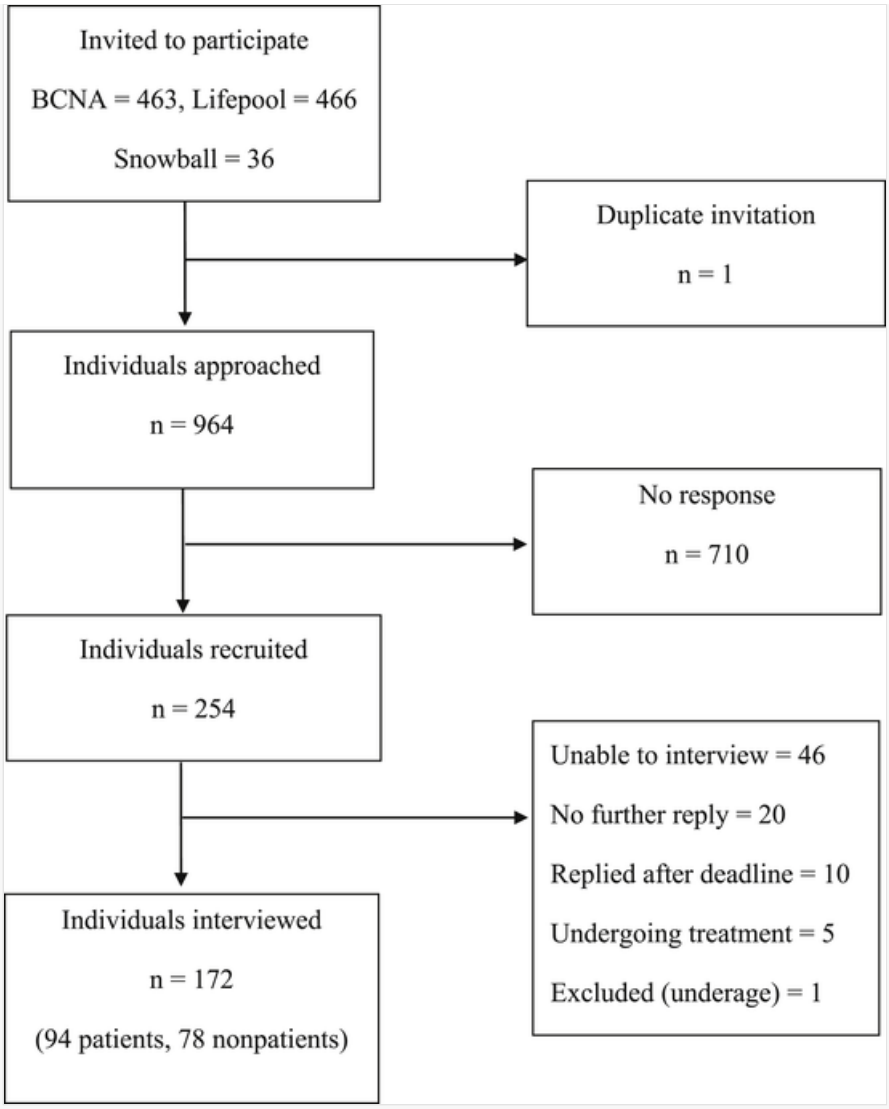
Fig. 1



A flow chart of patient recruitment and participation in the main study. BCNA: Breast Cancer Network Australia.

All 94 patients and 78 non-patients successfully completed the interview in full. Patients took longer on average (56 versus 45 min, $P < 0.001$), but there was no significant difference in questionnaire difficulty reported ($P = 0.296$). Socio-demographic characteristics were similar between the two groups (Table 1), although non-patients tended to have a higher risk threshold below which they were uncomfortable to consider active monitoring, reported less worry and were more likely to consider active monitoring than patients.

alt-text: Table 1

Table 1

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A comparison of participant demographics.

Demographic	% of Patients (n = 94)	% of Non-patients (n = 78)	P value
Age in years: Mean (SD)	66.2 (6.7)	58.7 (11.9)	**0.007
Education level:			
Secondary school	14 (15)	7 (9)	
Certificate or diploma	23 (25)	16 (21)	0.094
Undergraduate degree	19 (20)	29 (37)	
Postgraduate degree	38 (40)	26 (33)	
Socio-economic income:			
Low	12 (13)	6 (8)	
Middle	25 (27)	16 (21)	0.356
High	44 (46)	47 (60)	
Prefer not to say	13 (14)	9 (11)	
Relationship status:			
Single	9 (10)	13 (17)	
Married	67 (70)	52 (67)	0.432
Separated or divorced	10 (11)	6 (7)	
Widowed	8 (9)	5 (6)	
Prefer not to say	0 (0)	2 (3)	
Current employment status:			
Full or part time	40 (43)	42 (54)	
Unemployed	2 (2)	0 (0)	**0.032
Retired	48 (51)	28 (36)	
Carer, volunteer or other	4 (4)	8 (10)	
Ethnicity:			
Australian	69 (73)	61 (78)	
New Zealand/Torres Strait Islander	4 (4)	4 (5)	
European	11 (12)	6 (8)	0.286
Asian	3 (3)	5 (6)	
American	7 (8)	0 (0)	
Middle Eastern	0 (0)	2 (3)	

Attended breast screening	76 (81)	59 (76)	0.408
Undergone a breast biopsy	94 (100)	15 (19)	***0.000
Breast cancer diagnosis:			
DCIS	33 (35)	–	N/A
Invasive breast cancer	61 (65)	–	
Treatment received:**			
Breast conserving surgery	65 (69)	–	
Mastectomy	39 (41)	–	
Adjuvant radiotherapy	54 (57)	–	N/A
Endocrine therapy	56 (60)	–	
Chemotherapy	36 (38)	–	
Sentinel lymph node	56 (60)	–	
Worried about breast cancer:			
Not at all	23 (24)	32 (41)	
A little	49 (52)	35 (45)	**0.015
Some of the time	15 (16)	10 (13)	
A lot or all the time	7 (8)	1 (1)	
Difficulty of questionnaire			
Very easy or easy	44 (37)	35 (45)	
Neither easy nor difficult	19 (20)	12 (15)	0.296
Difficult or very difficult	31 (33)	31 (40)	
Would consider active monitoring?	57 (61)	76 (97)	***0.000
Mean % risk threshold for monitoring (SD)	84.0 (0.22)	72.0 (0.16)	***0.000

DCIS: ductal carcinoma *in situ*.
*Totals add up to greater than 100% as some patients received multiple treatments.

3.2 Utilities

Mean and median utilities are presented in Table 2. Utilities are scaled from 0 to 1, whereby values closer to 1 are indicative of a stronger preference for the health state. Overall, both patients and non-patients had the strongest preference for active monitoring followed by BCS, BCS with radiotherapy, mastectomy and lastly treatment for progression. The only exception was the VAS where BCS alone was rated more favourably by patients (0.61, SD 0.19). As expected, mean utilities for active monitoring increased as the risk of disease

progression decreased from 40% to 10%. Utilities for most health states describing DCIS were close to perfect health, as indicted by the upward skew, but more invasive treatments were associated with worse average quality of life (mastectomy: 0.454, BCS with radiotherapy: 0.575).

alt-text: Table 2

Table 2

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A summary of health state utility values by instrument and population.

Health state	VAS Mean (CI)	VAS Median (IQR)	SGMean (CI)	SGMedian (IQR)	EQ-5D Mean (CI)	EQ-5DMedian (IQR)
Breast conserving surgery alone						
Patients	0.691 (0.653–0.739)	0.703 (0.600–0.800)	0.820 (0.784–0.856)	0.900 (0.800–0.900)	0.767 (0.733–0.801)	0.768 (0.696–0.848)
Non-patients	0.623 (0.579–0.667)	0.649 (0.500–0.750)	0.740 (0.693–0.787)	0.800 (0.600–0.900)	0.800 (0.769–0.831)	0.817 (0.681–0.879)
Breast conserving surgery with radiotherapy						
Patients	0.615 (0.569–0.661)	0.638 (0.500–0.800)	0.790 0.752–0.828)	0.875 (0.700–0.900)	0.699 (0.661–0.737)	0.729 (0.592–0.837)
Non-patients	0.575 (0.533–0.617)	0.589 (0.474–0.706)	0.700 (0.653–0.747)	0.700 (0.600–0.900)	0.700 (0.658–0.742)	0.724 (0.592–0.837)
Mastectomy+/-reconstruction						
Patients	0.567 (0.521–0.613)	0.553 (0.400–0.750)	0.790 (0.752–0.828)	0.900 (0.700–0.900)	0.606 (0.560–0.652)	0.649 (0.531–0.748)
Non-patients	0.454 (0.405–0.503)	0.456 (0.300–0.600)	0.650 (0.599–0.701)	0.700 (0.500–0.800)	0.578 (0.527–0.629)	0.614 (0.510–0.728)
Active monitoring (40% risk of progression)						
Patients	0.547 (0.496–0.597)	0.550 (0.400–0.710)	0.850 (0.822–0.878)	0.900 (0.900–0.950)	0.819 (0.789–0.849)	0.848 (0.791–0.879)
Non-patients	0.696 (0.660–0.731)	0.700 (0.611–0.800)	0.870 (0.841–0.899)	0.900 (0.900–0.950)	0.840 (0.807–0.873)	0.879 (0.848–0.879)
Active monitoring (20% risk of progression)						
Patients	0.588 (0.537–0.639)	0.618 (0.450–0.800)	0.870 (0.844–0.896)	0.900 (0.900–0.950)	0.826 (0.794–0.858)	0.879 (0.848–1.000)

Non-patients	0.733 (0.700–0.766)	0.750 (0.680–0.850)	0.890 (0.866–0.914)	0.950 (0.900–0.950)	0.863 (0.836–0.890)	0.879 (0.848–1.000)
Active monitoring (10% risk of progression)						
Patients	0.645 (0.594–0.696)	0.693 (0.450–0.875)	0.880 (0.854–0.906)	0.900 (0.900–0.950)	0.863 (0.833–0.893)	0.879 (0.848–1.000)
Non-patients	0.775 (0.744–0.806)	0.800 (0.722–0.875)	0.900 (0.878–0.922)	0.900 (0.900–0.950)	0.884 (0.855–0.913)	0.879 (0.879–1.000)
Progressed DCIS to invasive breast cancer						
Patients	0.498 (0.445–0.551)	0.500 (0.300–0.700)	0.810 (0.776–0.844)	0.900 (0.700–0.900)	0.558 (0.501–0.615)	0.622 (0.388–0.745)
Non-patients	0.519 (0.470–0.568)	0.500 (0.313–0.700)	0.740 (0.691–0.789)	0.800 (0.600–0.900)	0.553 (0.493–0.613)	0.624 (0.422–0.736)

CI: 95% confidence interval; DCIS: ductal carcinoma *in situ*; EQ-5D: EuroQol-5 dimensions; SG: standard gamble; VAS: visual analogue scale.

The EQ-5D-5L demonstrated the most consistent ranking of health states. Fig. 2 reports the overall percentage of women reporting any perceived impairment in each EQ-5D dimension of quality of life. Utilities for active monitoring were primarily driven by anxiety/depression. In contrast, conventional treatments were perceived to impact upon other dimensions of health such as pain, self-care and usual activities. Consequently, utilities for surgery and radiotherapy were much lower than monitoring.

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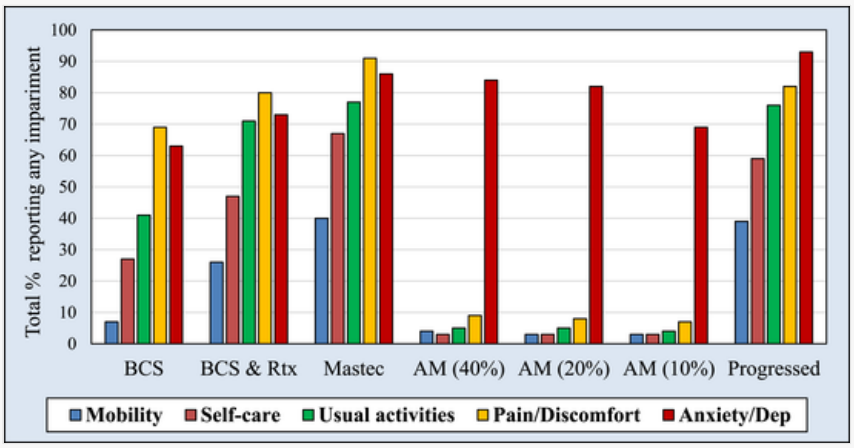
Fig. 2



Total percentage of women reporting any level of impairment in each of the EQ-5D-5L dimensions of quality of life for the seven health states. BCS: breast conserving surgery; Rtx: radiotherapy; Mastec: mastectomy; AM: active monitoring; Progressed: progressed DCIS; Dep: depression; DCIS: ductal carcinoma *in situ*; EQ-5D: EuroQol-5 dimensions.

Patients utilities were higher for conventional treatment using standard gambles (P = 0.005) and lower for active monitoring using VAS (P < 0.001), but there were no significant differences between the two groups for any health states using the EQ-5D-5L. Pairwise analysis demonstrated strong positive correlation between utilities for active monitoring (0.93, P < 0.001) but weak positive associations between monitoring and intensive management (0.25, P = 0.016), i.e. women with a preference toward monitoring tended to report lower utilities for a mastectomy and vice versa.

Regression demonstrated that socio-demographics accounted for <5% of the variability in utilities. Employment and financial status had a weak positive effect on mastectomy (P = 0.068). Having breast cancer or a lower baseline threshold for recurrence risk was associated with a lower utility for active monitoring (P < 0.001).

3.3 Quality appraisal

Although there are no quality checklists for utilities, it is important to assess whether the values are valid [30]. The utilities demonstrated good feasibility as reflected by the lack of missing data, high completion rate and consistency between methods. Descriptive validity was confirmed through extensive piloting, and the three methods demonstrated good convergent validity and consistency in ranking across the seven health states. Test–retest reliability among women participating in the pilot and main study were within expected levels of agreement [31] and few (6%) rated the tasks as 'very difficult' on a Likert scale.

4 Discussion

4.1 Principal findings

The results suggest that most women would find active monitoring an acceptable alternative to surgery for reducing the impact of overdiagnosis, if shown to be safe in clinical trials. Both patients and non-patients valued monitoring more favourably than surgery and radiotherapy on average. There was some individual heterogeneity suggesting that de-escalation may not be preferred by everyone, but regression suggests these are likely to be women with prior history of cancer or fear of progression.

The acceptability of active monitoring was highly dependent on risk of progression and perceived anxiety. Although on average, a 10% risk of progression in 10 years was an acceptable trade-off, some women were willing to accept the risk of possible side-effects from surgery or radiotherapy to reduce the risk of local recurrence. It is hard to predict the risk in an individual patient, and therefore, treatment is given in case it is beneficial [32]. This study shows that if the risk of progression is low, most women will choose observation; however, if the risk is high, that number is substantially reduced. Ultimately, the acceptability of active monitoring is dependent on defining these risks in clinical trials and communicating outcomes to patients.

There was considerable interpatient variation that could not be explained by the socio-demographic factors examined. Attitudes toward risk threshold [33], fear of recurrence [34] and disease knowledge vary widely [35] and support the hypothesis that the factors influencing preferences are complex. Little is known about attitudes toward active monitoring and further research to identify women who are likely to benefit from

conservative management is necessary. Gaining understanding of the risk of invasive progression will provide comfort for both patients and providers.

Overall, utilities were lower than in other studies, which have focused on the benefits of adjuvant radiotherapy [22,27] or valued *in situ* and invasive treatment concurrently [36]. In our study, women were provided with health states explicit in detailing the benefits and harms of active treatment, including the chance of overdiagnosis, which may explain the lower utilities observed. Women may express a higher utility to treatment where they believe that the treatment (and associated side-effects) are necessary or they believe they are lucky that the cancer has been found early and treated. Providing a more balanced assessment of the benefits and risk of treatment may better reflect the utility of treatment. Similarly, our methods are more likely to represent actual preferences than those elicited in clinical trials where women may not be able to trade-off the benefits and risks in surgical arms.

There are no published utilities for active monitoring in breast cancer, but the results are comparable to those elicited in prostate [37] and cervical cancer screening [38]. Active monitoring has been successfully implemented for other low risk cancers [39]. The utilities derived in this study show theoretical acceptability of DCIS surveillance and is encouraging information for clinicians looking to reduce the harms of overdiagnosis in the screening population.

4.2 Strengths and limitations

To the best of our knowledge, this is the first empirical study to value the quality of life associated with active monitoring for breast cancer. This is especially significant because it provides real-world data to suggest the acceptability of conservative approaches towards breast cancer treatment. Many women may find active monitoring a sensible alternative to surgery in terms of quality of life, which is likely to have significant implications for future health policy.

The methods used to elicit utilities were justified through rigorous systematic review. Health states were extensively piloted on clinical experts, academics and patients and explicitly included overdiagnosis, providing balanced information of the potential benefits and harms during the valuation process. This balance is important in addressing the limitations identified in a review of breast screening health states [18]. The instruments demonstrated convergent validity, but the VAS and EQ-5D are not truly ‘choice-based’ and may be constrained in conveying women's preferences towards hypothetical treatment.

There are limitations to any empirical research. The women recruited via cancer registries were likely more motivated and educated about breast cancer treatment. This study was unique in ascertaining the potential implications of de-escalating treatment from both a patient and population perspective but only included the views of women aged above ~~over~~ 30 years. Whether such preferences are transferable to the wider population may also depend on social normalities and perception of risk, particularly among younger women.

4.3 Future research and policy implications

Breast cancer treatment is moving towards a personalised, risk-based approach [40]. Whilst clinical trials may provide much needed clinical data on the value of de-escalating treatment, the potential policy implications of

adopting such approaches is unknown. More research is necessary to investigate the potential oncologic outcomes of balancing treatment with monitoring and what a surveillance protocol might look like beforeprior to offering it to patients. This research provides much needed data to inform the issues highlighted around the treatment of women likely subject to overdiagnosis and can be used to inform economic evaluations exploring personalised approaches to breast cancer screening and treatment.

5 Conclusion

Active monitoring for low-risk DCIS is an acceptable choice for most women. The findings suggest that improved quality of life through conservative management is as important to some women as reducing local recurrence during the trade-offs in the treatment decision. The magnitude of the utilities suggest that active monitoring may be as cost-effective as breast conservative surgery, but further assessment in an economic evaluation and clinical trial is required to validate this.

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Conflict of interest statement

None declared.

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Appendix ASupplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.09.026.

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Highlights

- This is the first study to value the QoL of active monitoring for breast cancer.
- Screen detected ductal carcinoma *in situ* (DCIS) may be subject to overdiagnosis and thus overtreatment.
- Women with low-risk DCIS would prefer less invasive treatment in terms of QoL.
- Active monitoring is valued an acceptable alternative to surgery and radiotherapy.
- More research is needed on how to de-escalate and balance the effects of treatment.

Appendix ASupplementary data

The following are the Supplementary data to this article:

Multimedia Component 1

Multimedia component 1

Queries and Answers

Query: Please confirm that given names and surnames have been identified correctly and are presented in the desired order and please carefully verify the spelling of all authors' names.
Answer: Names and order are correct. I might move the contact email to the section underneath as corresponding author. Also happy to change *corresponding author to Tracy E Roberts as I may be moving faculty shortly (Email: T.E.ROBERTS@bham.ac.uk)

Query: Your article is registered as a regular item and is being processed for inclusion in a regular issue of the journal. If this is NOT correct and your article belongs to a Special Issue/Collection please contact h.searle@elsevier.com immediately prior to returning your corrections.
Answer: Yes

Query: Please provide expansion, if any, for “BCNA” given in the artwork of figure 1.
Answer: BCNA: Breast Cancer Network Australia

Query: Please note that “**” and”***” are given in Table 1, but corresponding explanation is not provided in footnote. Kindly check and make necessary changes.

Answer: The * is labelled in the key. You may remove the ** and *** ones (they were displaying significance but this is self-explanatory)

Query: Have we correctly interpreted the following funding source(s) you cited in your article: Melbourne International Research Scholarship.?

Answer: Yes

Query: Please check the placement of section "Funding" and correct if necessary.

Answer: placement if fine

Query: Have we correctly interpreted the following funding source(s) and country names you cited in your article: National Breast Cancer Foundation, Australia?

Answer: Yes